Overview of Lung Cancer

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Lecture Goals

- Origin of Lung Cancer  
- Subtypes  
- New Treatment Paradigms in Lung Cancer

Causes of Lung Cancer

- Smoking  
  - 15-30x increased risk  
- Second hand Smoking  
- Radon Exposures  
- Work Place exposure  
  - Asbestos, silica, chromium, arsenic, diesel fuel  
- Genetic predisposition  
  - genes involved in cell cycle control or DNA damage repair  
- Prior Radiation therapy  
- Diet  

CDC, 2017
Lung Development

Differentiation of Respiratory Epithelium

- Lung produces more than 40+ types of cells
  - Basal cells → Squamous Cells carcinomas
  - Ciliated cells → Squamous Cell carcinomas
  - Type I/II pneumocytes → Adenocarcinomas
  - Clara cells → Adenocarcinomas/ Squamous Cell Carcinomas
  - Neuroendocrine cells → (atypical) carcinoids, SCLC, LCNEC

Travis et al. JTI Vol 6;2, 2011.

Lung Cancer Staging – TMN staging

Adenocarcinoma Spectrum

- Atypical Adenomatous Hyperplasia (AAH)
- Adenocarcinoma In Situ (AIS)
- Minimally Invasive Adenocarcinoma (MIA)
- Invasive Adenocarcinoma
- Invasive Mucinous Adenocarcinoma

Stage IB adenocarcinoma mixed subtype

Atypical Adenomatous Hyperplasia (AAH)

- Lepidic growth of atypical cells
- Can be isolated lesion versus multifocal disease

RADIOGRAPHIC FEATURES

- Peripheral
- Upper lobe
- ≤5 mm
- Spherical (76%)
- Slow growth rate
Adenocarcinoma In Situ (AIS)

- Pure lepidic growth
- Lacks invasion through basement membrane
- Transition lesion
  - AAH → AIS → IA

Radiographic Features:
- Irregular shape
- Predominantly ground glass opacity
- Internal air/cystic spaces
- Solid component should raise concern for invasion
- Slow growth

Minimally Invasive Adenocarcinoma (MIA)

- Predominantly lepidic growth
- Invasive component < 5mm
- 100% 5-year survival similar to AIS
  - 5-10mm: 70% 5-year survival
  - > 10mm: 60% 5-year survival

Radiographic Findings:
- Can be pure GGO
  - Impossible to differentiate from AIS
- Small solid component
  - < 5mm

Invasive Adenocarcinoma

- Multiple histologic subtypes
  - Lepidic (formerly BAC)
  - Acinar
  - Papillary
  - Micropapillary
  - Solid with mucin production
- > 5mm invasive component
  - Solid component

Adenocarcinomas

- Varied appearance
- Solitary pulmonary nodule → large mass
- Peripheral: central
- Upper lobes (3:2)
- Right lung (3:2)
- Ground glass is suggestive of lepidic component
- Lobulated vs spiculated
- Can lead to downstream obstructive pneumonitis

Adenocarcinoma – Solid with Mucin Production

- Goblet or columnar cell morphology
- Alveolar spaces distended with mucin
- > 50% harbor the Kras + mutation
- Solitary nodule
  - Excellent prognosis
- Resection
- Consolidation
  - May be multifocal
  - Aerogenous spread common
  - Satellite tumors
  - Lobar consolidation
  - May cavitate

Stage IV adenocarcinoma mucinous subtype

Stage III adenocarcinoma acinar subtype

Stage II adenocarcinoma ADC subtype

Stage IA adenocarcinoma

Stage IB adenocarcinoma

Stage IIA adenocarcinoma

Stage IIB adenocarcinoma

Stage IIIA adenocarcinoma

Stage IIIB adenocarcinoma

Stage IVA adenocarcinoma

Stage IVB adenocarcinoma

Stage IV adenocarcinoma mucinous subtype

Table: Pathology Findings

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pathology Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>Small (&lt;3 cm), consolidation, showing pure lepidic growth and occasionally micropapillary and solid components. Usually solid but may be mixed. The peripheral nodules of the peripheral component may be more solid but may not necessarily have a solid peripheral component.</td>
</tr>
<tr>
<td>IIIB</td>
<td>Larger (&gt;3 cm), showing more solid growth and often solid consolidation. Usually solid but may be mixed. The peripheral nodules of the peripheral component may be more solid but may not necessarily have a solid peripheral component.</td>
</tr>
<tr>
<td>IVA</td>
<td>Large (&gt;5 cm), showing more solid growth and often solid consolidation. Usually solid but may be mixed. The peripheral nodules of the peripheral component may be more solid but may not necessarily have a solid peripheral component.</td>
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<tr>
<td>IVB</td>
<td>Very large (&gt;7 cm), showing more solid growth and often solid consolidation. Usually solid but may be mixed. The peripheral nodules of the peripheral component may be more solid but may not necessarily have a solid peripheral component.</td>
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</table>

Squamous Cell Carcinomas

- 30-35% of lung cancer
- Strong association with smoking (inhaled exposure)
- Four subtypes
  - Papillary (best prognosis)
  - Clear Cell
  - Small Cell
  - Basaloid

RADIOGRAPHIC FEATURES
- Central location
- Peripheral nodules/mass (30%)
- Rapid Growth → central cavitation
- Common to have bronchial wall invasion
  - Infiltrates along airways
  - Bronchial wall thickening

Stage 2 squamous cell carcinoma

Squamous Cell Carcinoma in Situ

- Bronchial squamous dysplasia → precursor to SCC and Basaloid Cancer
- Strong association with smoking
- Propensity for large airway near bifurcations
- Clonal versus multifocal
- Mild → moderate → severe → CIS

Moderate squamous cell Dysplasia (HIV pt)

Pancoast tumor

- T3 tumor with chest wall invasion
- Rib/vertebral destruction
- Hand muscle atrophy (brachial plexus involvement)
- Horner’s syndrome – sympathetic ganglion invasion

Large Cell Carcinomas (LCC)

- < 10 %
- Lack histologic differentiation of squamous adenoc/ neuroendocrine
- Diagnosis of exclusion
- Many variants of LCC including
  - LCC with rhabdoid features
  - LCC with NE features
  - Clear Cell Carcinoma
  - Giant Cell Carcinoma

RADIOGRAPHIC FEATURES
- Large heterogeneous mass
  - Usually enhancing
- Round versus lobulated borders
- Calcifications present in 20% of lesions
- Regional adenopathy and distant mets often present

Large Cell Carcinoma with Sarcomatoid Features
Table 1. Spectrum of Neuroendocrine Proliferations and Neoplasms of the Lung

<table>
<thead>
<tr>
<th>NEUROENDOCRINE CELL HYPERPLASIA AND TUMORLETS</th>
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<tbody>
<tr>
<td>Neuroendocrine cell hyperplasia</td>
</tr>
<tr>
<td>• associated with fibrosis and/or inflammation adjacent to carcinoid tumors</td>
</tr>
<tr>
<td>• diffuse idiopathic neuroendocrine cell hyperplasia with or without airway fibrosis obstruction</td>
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<tr>
<td>Tumors With Neuroendocrine Morphology</td>
</tr>
<tr>
<td>• Typical carcinoid</td>
</tr>
<tr>
<td>• Atypical carcinoid</td>
</tr>
<tr>
<td>• Large cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td>• Small cell carcinoma</td>
</tr>
<tr>
<td>NSCLC With Neuroendocrine Differentiation</td>
</tr>
<tr>
<td>OTHER TUMORS WITH NEUROENDOCRINE PROPERTIES</td>
</tr>
<tr>
<td>Pulmonary blastoma</td>
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<tr>
<td>Primitive neuroectodermal tumor</td>
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<tr>
<td>Desmoplastic round cell tumor</td>
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<tr>
<td>Carcinomas with Rhabdoid Phenotype</td>
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<td>Paraganglioma</td>
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<th>Neuroendocrine Tumors</th>
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<tr>
<td>Tumor Staging system</td>
</tr>
<tr>
<td>TC TNM</td>
</tr>
<tr>
<td>AC TNM</td>
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<tr>
<td>LCNEC TNM</td>
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<tr>
<td>SCC Limited vs extensive disease</td>
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Diffuse Idiopathic Pulmonary Neuroendocrine hyperplasia (DIPNECH)

- Precursor lesion to pulmonary carcinoids
- Proliferation of neuroendocrine cell in the bronchial walls → leads to airway disease
- F>M, 50-60s.

RADILOGRAPHIC FEATURES
- Airways disease
- Nodules
  - <5 mm tumorlets
  - >5 mm Carcinoids

Carcinoids

TYPICAL CARCINOIDS
- Most common childhood CA
- Present earlier b/c 60-85% central location with sx
- Low grade
- Not associated with smoking
- Highly vascular

ATYPICAL CARCINOIDS
- Present later b/c of peripheral location n asx
- Intermediate grade
- Associated with smoking
- Larger, more invasive and vascular
- Early mets (osteoblastic bone, liver, brain, adrenal gland)

Large Cell Neuroendocrine Carcinomas

- 3% of all lung cancers
- Strong association with smoking
- Early metastasis
- Intermediate grade

RADILOGRAPHIC FEATURES
- Peripheral, 80% >4cm at presentation, well defined
- Commonly necrotic but rarely cavitate
- Heterogenous enhancement

Small Cell Lung Carcinoma (SCLC)

- Rapid Growth
- Considered metastatic at presentation (60-70% with metastatic disease)
- Strong association with smoking
- Pure SCLC versus combined SCLC

Staging SCLC (VASLG/IASCL)

- Limited stage (equivalent to TNM I-III)
  - Disease restricted to one hemithorax with regional lymph nodes:
    - Hilar ipsilateral and conlateral
    - Mediastinal ipsilateral and contralateral
    - Supraclavicular ipsilateral and contralateral
    - Ipsilateral pleural effusion (benign or malignant)
- Extensive stage (equivalent to TNM IV)
  - Sites of disease beyond that of limited disease.

RADIOGRAPHIC FEATURES

- Large hilar/perihilar central mass with extensive adenopathy
- Often difficult to see primary tumor
- Bronchial compression without endobronchial lesions
- Proximal growth along submucosa
- Extensive necrosis/hemorrhage but cavitation is rare

6 weeks following chemorads

Genetics of Lung Cancer

- Mutually exclusive mutations
  - EGFR
  - KRAS
  - ALK
- Varied response to Tyrosine kinase inhibitors


**Kras Mutations**

- Positive smoking history
- Less common in Asian population
- Worse prognosis
  - Biomarker for non/limited response to TKI
- More common in Adenocarcinomas
  - Uncommon in Squamous Cell Carcinoma

**EGFR mutations**

- More common in adenocarcinomas (micropapillary, lepidic predominant)
- F>M, middle age, Asian
- Non-smoking history
- Ex19 deletion, Ex21 L858R and Ex19 G719X – best response to TKI therapy
- Ex20 T790M associated with acquired resistance

**Adenocarcinoma EGR ex 19 deletion**

Pre TKI therapy | Post TKI therapy

**ALK rearrangements**

- ALK- EML4 fusion seen in 2-7% of NCSSLC
- Non-smokers/light smokers
- Mutually exclusive from EGFR
- Targeted Therapy (ALK inhibitors)
  - Crizotinib, ceritinib, brigatinib

**ROS/RET fusions rearrangements**

- Mainly observed in young females, non-smoking history
- Can be targeted by TKIs
  - ROS 1 shared structural similarity with ALK fusion

**TKI therapy**

- Median response rates
  - EGFR
    - Gefitinib – 6-9 months
    - Erlotinib – 9-10 months
    - Afatinib – 11-13 months
  - ALK Fusion
    - Ceritinib – 24 months
    - Crizotinib – 18 months
- Increase pressure for new mutations (resistance)
- Always look at pre-treatment scans when assessing disease progression
EGFR+ AdenoCA on TKI therapy

Pre treatment 4 months 12 months 18 months

Immunotherapy (Check point Blockade)

- Designed to activate the immune system
- PD1 inhibitors —
  - Pembrolizumab (keytruda)
  - Nivolumab (opdivo)
- PD-L1 inhibitors
  - Atezolizumab, avelumab, durvumab
- CTLA-4 inhibitors
  - ipilimumab

Unique Response Patterns with Immunotherapy

- Reduction in the tumor size
  - Similar to cytotoxic therapy
- Pseudoprogression
- Mixed response to disease
- Prolonged Stable disease

Pseudoprogression

Immune related Adverse Effects (irAEs)

- Dermatologic/Mucosal
- GI manifestations (diarrhea, colitis)
- Hepatotoxicity
- Pneumonitis
- Endocrinopathies
- Less common
  - Kidney
  - Hematologic
  - Cardiotoxic
  - Neurologic

Drug Toxicity - Pneumonitis

RADIOLOGIC FINDINGS

- Ground Glass
- Organizing Pneumonia
- Diffuse Alveolar Damage
- Hypersensitivity
  - Pneumonitis
- Nonspecific Interstitial Pneumonia

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